

STRONTIUM 89 FOR PALLIATION OF BONE METASTASES

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At the University of Kansas Medical Center, systemic use of strontium 89 (^{89}Sr), a beta-emitting radioisotope, was evaluated in the treatment of metastatic carcinoma to bone for relief of bone pain. Eighty-five patients were treated with systemic ^{89}Sr in the dosage of 30 to 40 $\mu\text{Ci/kg}$. All patients had multiple bone metastases, the majority with primary breast or prostatic cancer. The response to treatment was evaluated by daily diary entries, changes in the amount of pain medication, periodic bone scans, and other laboratory values.

In the patients who survived (47) and who were observed for three or more months, overall results showed 15 percent becoming pain free; 23 percent showed marked improvement with decreased consumption of pain medication; 53 percent showed mild but significant improvement in pain relief and decrease in pain medication requirement; and 9 percent showed no improvement. No patients noted a worsening of bone pain after the treatment. There was a combined favorable

response in 91 percent (43/47) of patients with some meaningful palliation after ^{89}Sr therapy. This study, using ^{89}Sr systemic therapy, suggests that this isotope may be a valuable adjuvant therapy for palliation of pain from metastatic bone lesions.

Bone metastases are commonly observed with malignant tumors, most commonly from prostatic carcinoma in men and breast carcinoma in women. In clinical oncology the management of disseminated bone metastases is always a challenge. Long-term treatment of pain from bone metastases creates serious problems. If the process is localized, radiotherapy is the method of choice.

Hormonal treatment, either by bilateral orchiectomy or estrogen therapy, is the most widely used therapy for disseminated prostatic carcinoma. However, some patients, after a period of symptomatic relief of pain, fail to respond to conservative therapy. For patients with disseminated breast carcinoma, chemotherapy is being used widely, but generally it is not effective for bone pain from diffused metastases.

Lawrence and Tobias¹ were the first to use radioactive phosphorus (^{32}P) on neoplastic tissues. Later, ^{32}P was used for palliation of pain from bone metastases.²⁻⁷ In recent years, hemi-body or total body radiation^{8,9} has also been tried. Because of poor tolerance to external radiation and hematological complications of ^{32}P therapy, these treatment techniques are not widely used.

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TABLE 1. STRONTIUM 89 THERAPY

Tumor Histology	No. of Patients
Adenocarcinoma of prostate	53
Adenocarcinoma of breast	18
Osteogenic sarcoma	3
Adenocarcinoma of colon	2
Adenocarcinoma of lung	2
Primary unknown	2
Ewing's sarcoma	1
Renal cell carcinoma	1
Neuroblastoma	1
Clear cell carcinoma of ovary	1
Duodenal adenocarcinoma	1
Total	85

Firusian¹⁰ made an interesting observation. While obtaining scintigrams of bones using strontium 85, he noticed some analgesic effect in a number of patients suffering from bone metastases. This observation prompted investigation of the beta-emitting strontium 89 radioisotope. Firusian used ⁸⁹Sr at a dose of 30 μ Ci/kg in 11 patients with prostatic carcinoma. A significant and lasting improvement in the relief of bone pain was seen in eight of 11 patients. These encouraging results prompted us at the University of Kansas Medical Center to evaluate strontium 89 in the palliative management of bone pain due to metastatic disease.

Strontium is a calcium analog. The metabolism of strontium is similar to the metabolism of calcium, thus the affinity of strontium to the bones. It is estimated that 50 percent of the injected dose remains in the body, with 70 percent of the retained isotope being stored throughout the bony skeleton.¹¹ Strontium 89 is a pure beta emitter with a maximum beta energy of 1.46 MEV. It has a physical half-life of 52 days. The radiation absorbed dose^{10,11} to the entire skeleton, when administered at a dose of 30 μ Ci/kg of body weight, is approximately 1,000 rad, assuming there is a uniform distribution throughout the skeleton. There is significant sparing of the bone marrow with ⁸⁹Sr with a calculated marrow dose of less than 6 to 11 rad.¹¹ This is due to the relatively

selective uptake of strontium in bone and the fact that there is no significant gamma radiation. Patients with widespread metastatic involvement should have up to five times greater uptake of strontium than the surrounding normal bone, resulting in a redistribution of the isotope in patients with metastatic disease, giving substantially greater radiation to the metastatic sites and less radiation to normal bone.

METHODS AND MATERIALS

At the University of Kansas Medical Center, a pilot study was initiated in 1977 to evaluate the effectiveness of ⁸⁹Sr for palliation of pain from disseminated metastatic bone disease. Patients were initially entered into the protocol when other accepted modes of therapy had proven unsuccessful. Patients were symptomatic from metastatic bone disease. There was histologic proof of the primary malignancy and evidence of bone metastases by bone scan or x-rays. Concomitant external radiation therapy was used for metastatic disease in weight-bearing bones to prevent pathological fractures.

A total of 85 patients have been treated between 1977 and 1983. Most of these patients were with primary prostatic or breast cancer (Table 1). Initially the first 20 patients were treated at a dose of 30 μ Ci/kg of body weight and strontium is administered intravenously in the chloride form. Because of encouraging results in evaluable patients with this dose, and because no significant bone marrow depression was observed in these patients that could be attributed to strontium, the dose was escalated to 40 μ Ci/kg of body weight. This dose was used in additional 65 patients.

The evaluation of response was determined by both subjective and objective methods. As the evaluation of pain is subjective, a carefully defined protocol was followed, which had been standardized previously for the evaluation of pain in clinical pharmacology. The patients maintained a daily diary, and the patient was asked to rate the degree of pain as mild, moderate, or severe. The objective response was evaluated by careful evaluation of

TABLE 2. STRONTIUM 89 THERAPY: OVERALL RESPONSE OF TREATMENT ACCORDING TO DOSE ($\mu\text{Ci/kg}$)

Response	30 $\mu\text{Ci/kg}$	40 $\mu\text{Ci/kg}$	Total
Worsening of symptoms	0	0	0
No improvement	0	4	4
Mild decrease in pain	6	19	25
Marked decrease in pain	2	9	11
Pain free	2	5	7
Totals	10	37	47

TABLE 3. ^{89}Sr THERAPY: RESPONSE OF TREATMENT IN EVALUABLE PATIENTS (n=47)

Response	No. of Patients (%)
Worsening of symptoms	0/47 (0)
No improvement	4/47 (9)
Mild decrease in pain	25/47 (53)
Marked decrease in pain	11/47 (23)
Pain free	7/47 (15)
Total Favorable Responses	43/47 (91%)

increase or decrease in pain, amount of pain medication required (patients recorded the number of tablets taken daily in their daily diary), and serial laboratory and x-ray examinations, including complete blood count with platelet count, alkaline phosphatase, acid phosphatase (in prostatic cancer patients), calcium, phosphorus, whole-body bone scan, and x-rays of known metastases.

RESULTS

A total of 85 patients have been treated to date. Of these 85, a fairly large number (38) did not sur-

vive beyond three months following their initial treatment, or were lost to follow-up, or had been treated within the last three months prior to review of this data. The relatively high death rate in the initial months following treatment is primarily a reflection of the late stage of the patient's disease prior to referral for strontium therapy. These patients were not considered in the analysis of the data. The remaining 47 patients form the basis for this report. In the patients who survived and who were observed for three or more months, overall results showed 15 percent becoming pain free, 23 percent showed marked improvement with decreased consumption of pain medication, 53 percent showed mild but significant improvement in

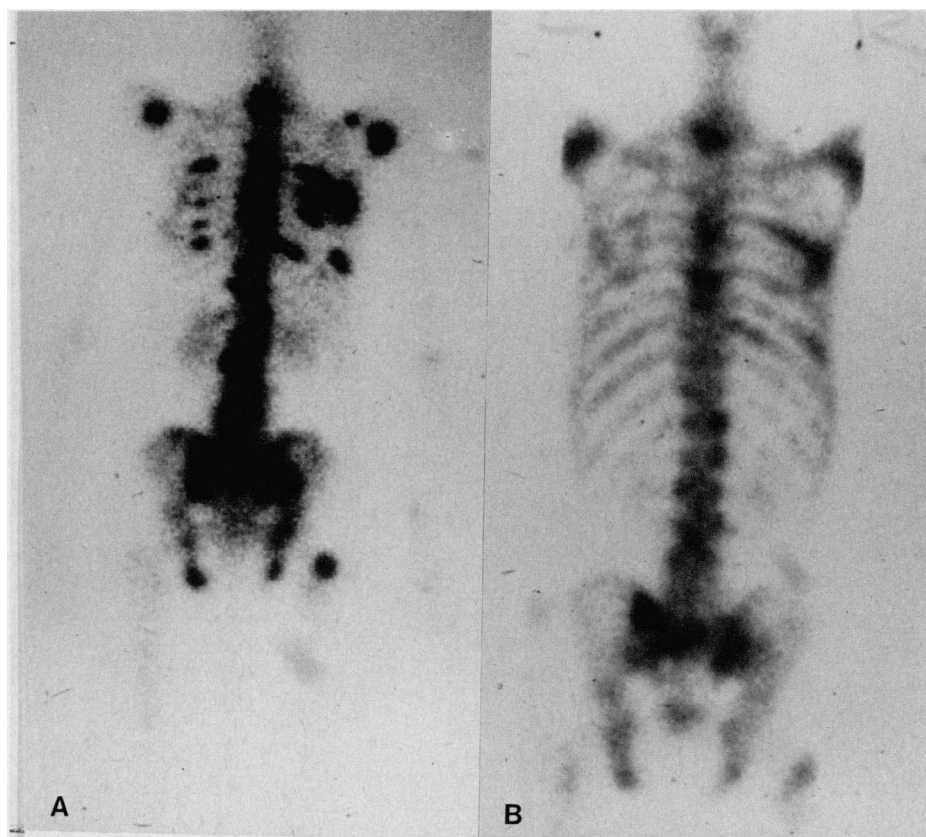


Figure 1. A 60-year-old man with widespread bone metastases from prostatic carcinoma. (A) Bone scan of posterior view, July 1979. (B) Bone scan of posterior view, February 1980, after administration of strontium 89

pain relief and decrease in pain medication requirement, and 9 percent showed no improvement (Table 2). No patients noted a worsening of bone pain after the treatment. There was a combined favorable response in 91 percent (43/47) of patients with some meaningful palliation after strontium 89 therapy (Table 3). The patients showing the greatest relief had a second course of strontium three months after the first dose. Some of these patients showed marked improvement in the follow-up bone scan (Figures 1 and 2).

DISCUSSION

Carcinoma of the breast is the most common cancer affecting women over the age of 40 years.

And carcinoma of the prostate is the second most common carcinoma in men. Both commonly metastasize to bone and often present with multiple bone metastases as the primary clinical problem, with little or no soft tissue disease. Management of bone metastases and the associated pain is a major clinical problem. Several treatment approaches such as orchiectomy, estrogen therapy, and chemotherapy have been tried for metastatic carcinoma of prostate, and combination chemotherapy and sometimes bilateral oophorectomy, adrenalectomy, or hypophysectomy is used for metastatic female breast cancer. Unfortunately, none of the above offers long-term palliation for bone metastases.

For localized symptomatic bone metastases, the treatment of choice for palliation of bone pain is radiotherapy. For disseminated bone metas-

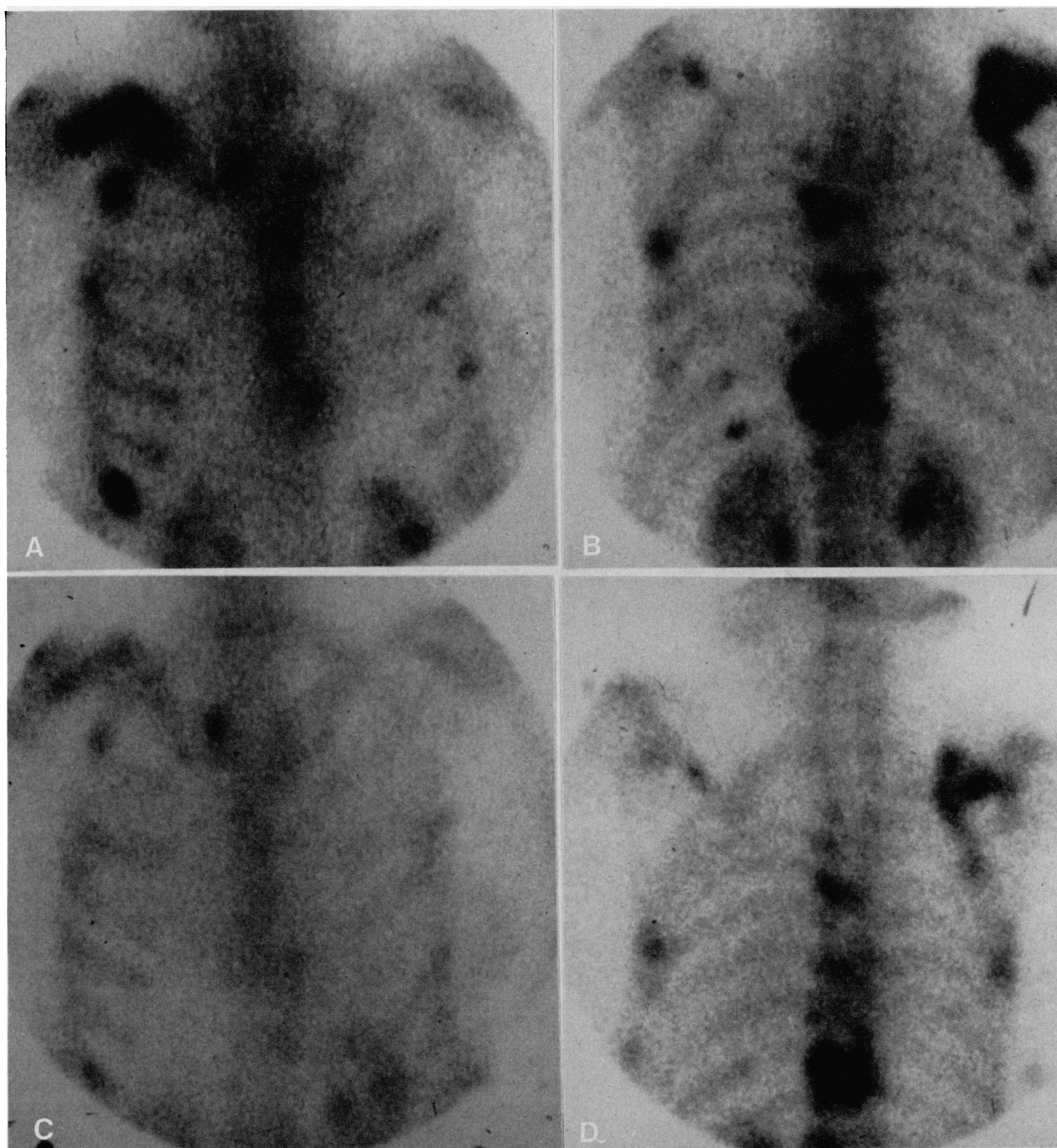


Figure 2. A 78-year-old woman with widespread breast carcinoma to bones. (A, B) Bone scans of anterior and posterior views, September 1981. (C, D) Bone scans of anterior and posterior views, August 1982, after administration of strontium 89

tases, the systemic radioisotope therapy has been used. Lawrence and Wasserman¹² used phosphorus 32 and strontium 89 in myeloma patients. Later, several investigators²⁻⁷ published their re-

sults of ^{32}P in patients with disseminated bone metastases. The main complication of ^{32}P therapy is severe myelosuppression. In recent years hemi-body or whole-body radiation for wide-

spread bone disease has been used.^{6,9} Because of poor tolerance of patients to this type of therapy, these treatment techniques are not widely used.

Although Lawrence and Wasserman¹² used ⁸⁹Sr for the first time, they used this isotope along with phosphorus 32; hence, no valid conclusion could be drawn about the efficacy of ⁸⁹Sr in the treatment of patients with widespread bone metastases. Later Firusian and associates^{10,13} reported their results of ⁸⁹Sr treatment in different kinds of malignancies with bone metastases. In a recent report, Firusian et al¹⁰ reported a significant clinical improvement in eight of 11 patients (72 percent) with metastatic carcinoma of prostate to bone at a dose of 30 μ Ci/kg of body weight. Correns et al¹⁴ published their results on 20 patients; eight patients showed excellent relief of pain shortly afterward, and in eight others it was possible to pre-

vent the development of pain. Moderate improvement in three patients and a failure to provide relief in one were observed. In this pilot study there were 85 patients; 38 patients were excluded from analysis because of early death of patients after treatment, or were lost to follow-up, or were treated within the last three months prior to this analysis. Of the remaining 47 patients, a meaningful palliation was seen in about 91 percent of the patients (Table 3).

This study and other studies suggest that strontium 89 may be a valuable adjuvant therapy for palliation of pain from metastatic bone lesions. There is no evidence of bone marrow suppression attributable to this isotope from this study and other studies. For these reasons, ⁸⁹Sr may prove superior as a systemic radioisotopic treatment for metastatic cancer to the skeleton.

Literature Cited

1. Lawrence JH, Tobias CA. Radioactive isotopes and nuclear radiations in the treatment of cancer. *Cancer Res* 1950; 16:185-193.
2. Donati RM, Ellis H, Gallagher NI. Testosterone potentiated P₃₂ in prostate carcinoma. *Cancer* 1966; 19:1088-1090.
3. Friedell HL, Storaasli JP. The use of radioactive phosphorus in the treatment of carcinoma of the breast with widespread metastases to bone. *Am J Roentgenol* 1950; 64:559-575.
4. Maxfield JR Jr, Maxfield JGS, Maxfield WS. Use of radioactive phosphorus and testosterone in metastatic bone lesions from breast and prostate. *South Med J* 1958; 51:320-328.
5. Morales A, Connolly JG, Burr R, Bruce AW. The use of radioactive phosphorus to treat bone pain in metastatic carcinoma of the prostate. *Can Med Assoc J* 1970; 103:372-373.
6. Smart JG. The use of P₃₂ in the treatment of severe pain from bone metastases of carcinoma of the prostate. *Br J Urol* 1965; 37:139-147.
7. Wildermuth O, Parker D, Archambeau JO, Chanbazian C. The management of diffuse metastasis from carcinoma of prostate. *JAMA* 1960; 172:1607-1610.
8. Fitzpatrick PJ, Rider WD. Half-body radiotherapy. *Int J Radiat Oncol Biol Phys* 1976; 1:197-207.
9. Saenger EL, Silberstein EB, Aron B, et al. Whole body and partial body radiotherapy of advanced cancer. *Am J Roentgenol Radium Ther Nucl Med* 1973; 117:670-685.
10. Firusian N, Mellin P, Schmidt CG. Results of strontium 89 therapy in patients with carcinoma of the prostate and incurable pain from bone metastases: A preliminary report. *J Urol* 1976; 116:764-768.
11. Firusian N. Kinetik des Radiostrontium. *Nuklearmedizin* 1974; 13:127-128.
12. Lawrence JH, Wasserman LR. Multiple myeloma: A study of 24 patients treated with radioactive isotopes (P₃₂ and Sr-89). *Ann Intern Med* 1950; 33:41-55.
13. Firusian N, Schmidt CG. Radioisotopen—Therapie Maligner Skeletterkrankungen. *Nuklearmedizin (suppl)* 1974; 12:626-631.
14. Correns HJ, Mebel M, Buchali K, et al. Strontium 89 therapy of bone metastases of carcinoma of the prostate gland. *Eur J Nucl Med* 1979; 4:33-37.